33. (NEW) The method of claim 27, 31 or 32, wherein the agent is selected from the group consisting of an anti-TGF-β antibody, a PDGF and an RGD-containing peptide.

33 cont.

34. (NEW) The method of claim 33, wherein the RGD-containing peptide is GRGDSP.

REMARKS

Withdrawing Finality of Rejection

Under 37 C.F.R. §1.129, because this submission is timely filed with the appropriates fees, the finality of the final rejection is automatically withdrawn.

Status Of The Claims

Claims 1, 2, 5 to 7, 10, 13 to 15, 19 and 20 have been canceled. Claim 26 has been canceled. Claims 21 to 25 and 27 to 29, added in the parent application, are pending. New claim 30 has been added in the instant amendment.

The Restriction Requirement

The instant application is a rule 1.62 FWC of application U.S. serial no. 08/196,892; which itself is a rule 1.62 FWC of U.S. serial no. 07/416,656, filed October 3, 1989. Accordingly, the election made in the grandparent applies to the instant application. Applicants clarified the Restriction Requirement mailed July 3, 1991, in a telephone conference with the Examiner, as described in Applicants' written response dated August 30, 1991. Applicants elected with traverse the treatment claims of Groups I, II and III, directed to treatment with antibodies, PDGF and peptides.[1] The Examiner required a further election of species from Group I, II or III. The species of Group I directed to antibodies was elected.

Summary Of The Pending Claims

Claim 21 claims a method of treating a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of an extracellular matrix component in a tissue, comprising contacting the tissue with an agent that binds to TGF-β whereby the binding of the agent to the TGF-β suppresses the deleterious accumulation of the TGF-β-induced

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[1] The elected claims, including original claims 1, 5, 6, 10 and 13 to 15, were regarded as generic treatment claims.

extracellular matrix component in the tissue; and whereby the suppression of the deleterious accumulation of the extracellular matrix component treats the pathology or condition.

Claim 27 claims a method of decreasing the deleterious accumulation of a TGF-β induced extracellular matrix component in a tissue, comprising contacting the tissue with an agent which decreases the activity of TGF-β; or contacting the tissue with an agent which inhibits the extracellular matrix component-inducing activity of TGF-β; whereby the decrease in the activity of the TGF-β, whereby the decrease in the activity of the TGF-β decreases the deleterious accumulation of the extracellular matrix component; and whereby the agent is not a general protein synthesis inhibitor.

Claim 31 claims a method of decreasing the synthesis of a TGF-β by a cell in a tissue which produces the TGF-β, comprising contacting the tissue with an agent which decreases the activity of TGF-β; and whereby the decreased activity of TGF-β decreases the synthesis by the cell of the TGF-β.

Claim 32 claims a method of treating a pathology or a condition characterized by the TGF-β-induced deleterious accumulation of an extracellular matrix component in a tissue, comprising contacting the tissue with an agent which decreases

the activity of TGF-β; or contacting the tissue with an agent which inhibits the extracellular matrix component-inducing activity of TGF-β; whereby the decrease in the activity of the TGF-β decreases the deleterious accumulation of the extracellular matrix component.

Support for the Amendment to the Specification

The Specification sets forth an extensive description of the invention in the new and amended claims, and, for example, support may be found, *inter alia*: in the language of the Specification and the Abstract: pages 8 to, lines 4 to 37 and 1 to 14, respectively; page 9, lines 1 to 26; page 13, lines 17 to 29; pages 24 to 25, lines 34 to 37 and 1 to 19, respectively.

Applicants respectfully submit that the subject matter encompassed by the new and amended claims are adequately described in the Specification as submitted. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Obvious-type Double Patenting Rejections

Claims 21 to 29 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting

as being unpatentable over claims 1 to 4, 8, 27 and 30 of copending SN 07/467,888.

Claims 21 to 29 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 to 8 and 12 to 24 of copending SN 07/803,285.

Applicants will hold this issue in abeyance until such time a patent issues.

Objections to The Specification And Rejections to The Claims Under 35 U.s.c. § 112, First Paragraph

The Office Action has objected to the Specification and rejected claims 21 to 29 under 35 U.S.C. § 112, first paragraph, alleging that the Specification has failed to provide an enabling disclosure.[2] Applicants respectfully traverse this objection and rejection.

Section 112, 1st Paragraph, Requirements of Operability and Utility are Satisfied by the Specification

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[2] Please see page 2, lines 27 to 28, of the outstanding Office Action dated April 1, 1996, which maintained the rejection under section 112, first paragraph, set forth in the last Office Action dated June 2, 1994, for the parent, serial no. 08/196,892, on page 2, lines 22 to 26.

Specifically regarding claims 21 and 27, the Office Action alleges that because the disclosure describes treating excised nephritic tissue with antibodies and failed to disclose treating nephritic tissue with any and all other agents, it is not apparent agents would inhibit TGF-β activity in a manner or extent similar to the antibody used.[3] Applicant respectfully traverse.

The Patent Office is essentially challenging the operability, or utility, of the methods of the invention as useful and efficacious treatments. However, to maintain an objection or rejection based on lack of operability or utility, the Patent Office must provide evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility or that the nature of the invention is inherently unbelievable or involves implausible scientific principles. The Office Action has the initial burden of challenging a presumptively correct assertion of utility of the disclosure.[4]

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[3] Please see page 3, lines 1 to 7, of the Office Action dated June 2, 1994, serial no. 08/196,892. The Office Action alleges the claims must be limited to use of the antibody, please see line 7.

[4] [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling

The Office Action has proffered no evidence that a skilled artisan could not practice the invention utilizing the disclosure and guidance from the state of the art by analogy or prior art teachings without undue experimentation, as it pertains to a method of treating a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of an extracellular matrix (ECM) component in a tissue; a method of decreasing the deleterious accumulation of a TGF-β-induced extracellular matrix component in a tissue; or, a method of decreasing the synthesis of a TGF-β by a cell in a tissue which produces the TGF-β. No experimental data or scientific theories alleging that the invention is inherently unbelievable or involves implausible scientific principles has been presented.[5] Accordingly, a *prima facie* case of nonenablement has not been

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support . . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. (emphasis in original). *In re Marzocchi*, 439 F.2d 220, 223-224, 169 USPQ (BNA) 367, 369-70 (CCPA 1971). *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

[5] This rejection had been withdrawn by the previous Examiner, but reinstated by the new Examiner in the instant Office Action, please see page 3, lines 10 to 12. However, the instant Office Action, in reinstating the rejection, cites no art or data to support its statement rebutting the Specification's presumption of utility.

established and the objection and rejection can properly be withdrawn.

However, assuming *arguendo* that the Patent Office may have met this initial burden, Applicants respectfully maintain that they are able to offer sufficient rebuttal evidence and argument to convince one of skill in the art that methods of the instant invention satisfy section 112, first paragraph's requirements of operability and utility.

Applicants maintain that, based on the instant disclosure, one skilled in the art would reasonably expect that agents that can inhibit TGF-β activity would cause the same physiologic effect as that caused by the inhibition of TGF-β activity using an anti-TGF-β antibody. First, Applicants would like to emphasize it is not necessary or claimed that the agents that inhibit the activity of TGF-β within the scope of the invention need act in a manner or extent similar to the anti-TGF-β antibody.[6] In another words, the agents that inhibit the activity of TGF-β within the scope of the invention need not bind to TGF-β to effect that inhibition. The disclosed agents can act by any biological mechanism, such as, for example, blocking TGF-β

[6] Please see page 3, lines 1 to 7, of the June 2, 1994, Office Action, which alleges that "[i]t is not apparent that any and all other "agents" would inhibit TGF-β activity in a manner or extent similar to the antibody used."

from interacting with its cell surface receptor. To sufficiently describe and enable a method using an agent which inhibits TGF-β activity, it is not necessary that the disclosure prove or speculate on the possible biological mechanism(s) of such action.

Applicants maintain that the Specification sufficiently describes agents that inhibit the activity of TGF-β to satisfy the requirements of section 112, first paragraph. For example, Figure 4 demonstrates the effect of platelet derived growth factor (PDGF) on the increased proteoglycan synthesis induced by TGF-β. PDGF blocked the TGF-β-induced increase in proteoglycan production.[7] Furthermore, Example VIII discloses that RGD-containing peptides can inhibit the activity of TGF-β. Specifically, the peptide GRGDSP blocked the increased proteoglycan synthesis caused by the addition of TGF-β to the mesangial cell cultures.[8] Mechanistically, neither the PDGF nor the RGD-containing peptide bind TGF-β in a manner analogous to the binding of anti-TGF-β antibody to TGF-β. However, both inhibit the activity of TGF-β sufficiently to practice the methods of the invention. Applicants maintain that it is not

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[7] Please see page 13, lines 19 to 29; page 3, lines 19 to 25; and, Figure 4. The experiment illustrated in Figure 4 used cultures of rat mesangial cells labeled with 35 S methionine and treated with various growth factors, see page 3, lines 9 to 12.

[8] Please see page 8, lines 25 to 37; page 13, lines 17 to 29; and pages 24 to 25, lines 30 to 37 and 1 to 20, respectively, of the Specification.

necessary that the TGF-β-inhibiting agents of the invention operate in a manner similar to anti-TGF-β antibody and that TGF-β-inhibiting agents other than antibodies are described and enabled by the Specification commensurate with the scope of the claims. Accordingly, section 112 does not require the claims to be limited to anti-TGF-β antibodies.

The Office Action also alleges that the Specification fails to present evidence that any other proteins [other than biglycan and decorin] were studied and that TGF-β stimulates their synthesis. Specifically, it is alleged that the Specification fails to provide evidence regarding the increase or decrease in the glycoproteins other than decorin and biglycan, and merely because tissue "stained" does not indicate that TGF-β induced expression of any one particular glycoprotein over any other unless that glycoprotein were studied *per se*.[9] Therefore, the Office Action alleges the claims must be limited to biglycan and decorin.[10] Applicants respectfully traverse, noting first that the claims as amended do not read on a method for the

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[9] In the Office Action dated June 2, 1994, page 3, lines 23 to 29, it is noted that "Applicants have argued that PAS stains glycoproteins in tissues thus allowing one to visualize the extracellular matrix and that therefore the data do not indicate that accumulation of decorin and biglycan were exclusively suppressed." The Office Action is referring to statements made in the Preliminary Amendment, dated February 11, 1994, pages 4 to 5.

[10] Please see pages 3 and 4, lines 23 to 29 and 1 to 3, respectively, of the June 2, 1994, Office Action.

suppression of the ECM. The instant claims now read on a method of treating a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of an ECM component in a tissue; a method of decreasing the deleterious accumulation of a TGF-β-induced ECM component in a tissue; and, a method of decreasing the synthesis of a TGF-β by a cell in a tissue which produces the TGF-β.

Furthermore, the claimed methods do not read on or require the decrease in accumulation of any particular molecular specie of the ECM. The utility of the methods depend on decreasing the deleterious accumulation of the total ECM when that accumulation is caused by the cytokine TGF-β. The experiments disclosed in the Specification in fact demonstrate that inhibition of TGF-β activity decreases the overall amount, or deleterious accumulation, of ECM. For example, the amount ECM in an animal in which glomerular injury had been induced was quantitated using an established procedure well known to the skilled artisan. Specifically, to quantitate the amount of mesangial matrix, kidney tissue was processed and analyzed with periodic acid Schiff (PAS), which stains all glycoproteins in the ECM.[11] Matrix glycoprotein components include fibronectin, laminin, entactin, thrombospondin and collagen types I, III, IV

[11] Please see page 17, lines 11 to 30, of the Specification.

and V, in addition to proteoglycans.[12] After inducing an acute form of mesangial injury in the form of a glomerulonephritis, ultrastructural analysis confirmed an increase in mesangial ECM.[13]

The Specification also demonstrates that addition of TGF-β induces a dramatic increase in the production of proteoglycans in cultured mesangial cells[14] and that the ability to stimulate proteoglycan production is a relatively specific property of TGF-β.[15] The major proteoglycan species produced by mesangial cells were shown to be chondroitin/dermatan sulfate proteoglycans.[16] The major specie of proteoglycan produced by the cultured mesangial cells were identified as biglycan and decorin.[17] Animals with induced kidney injury treated with anti-TGF-β antibody had less ECM than control-treated, injured

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[12] Please see page 8, lines 17 to 24, of the Specification.

[13] Please see page 18, lines 2 to 19, of the Specification.

[14] Please see page 12, lines 25 to 37, of the Specification.

[15] Please see page 21, lines 9 to 10, of the Specification.

[16] Please see page 15, lines 25 to 37, of the Specification.

[17] Please see pages 22 to 23, lines 8 to 36 and 1 to 31, respectively, of the Specification.

animals.[18] Biochemical analysis showed that biglycan and decorin production by glomerular cells, which is high in injured kidneys, was suppressed by anti-TGF-β antibody.[19]

Additionally, independent scientific investigations have demonstrated that TGF-β is responsible for fibrinogenesis in some pathologies. For example, Fausto, N., *et al.*, *Ciba Foundation Symposium* 157 :165-174(1991)[20] concludes:

> The highly significant correlation between the expression of hepatic TGF-β1 mRNA and the various indices of fibrogenesis suggests that TGF-β1 plays an important role in the development of fibrosis in chronic liver disease.[21]

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[18] Please see page 24, lines 3 to 16, and Figure 17, of the Specification. The "control-treated" animals were injected with normal rabbit serum (versus immune serum containing anti-TGF-β antibodies).

[19] Please see page 24, lines 9 to 29, and Figure 18, of the Specification.

[20] Hereinafter "Fausto." Fausto was included in an IDS submitted with Applicants' response dated June 11, 1993, in the grandparent application no. 07/416,656; and discussed on pages 6 and 7 of that response.

[21] Please see page 172, "TGF-β and liver fibrosis," particularly the third paragraph, of Fausto.

Van Obberghen-Schilling, E.V., *et al.*, *J. of Biol. Chem.* 263 7741-7746 (1988)[22] illustrates that, at the time the instant application was filed, it was well known that TGF-β1 induces the synthesis of ECM components:

> As has been shown previously, TGF-β1 markedly enhances the formation of extracellular matrix by directly stimulating the synthesis of major matrix proteins such as collagen (10,11,36,37) and fibronectin (10, 37).[23]

Accordingly, Applicants maintain that section 112 does not require the methods to be limited to a claim reading on a method of treating a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of decorin and biglycan in a tissue or a method of decreasing the deleterious accumulation of a TGF-β-induced decorin and biglycan a tissue. However, Applicants acknowledge the Office Action's statement that claims with these embodiments do meet the requirements of section 112.

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[22] Hereinafter "Obberghen-Schilling." Obberghen-Schilling was expressly incorporated by reference into the Specification, please see page 24, lines 20 to 23; and for the Examiner's convenience, is attached herein as Exhibit A.

[23] Please see page 7745, *Discussion*, first paragraph, of Obberghen-Schilling. The references cited in the quoted passage as 10, 11, 36 and 37, are Ignotz, R.A., *et al.*, *J. Biol. Chem.* 262:6443-6446 (1987); Rossi, P., *et al.*, *Cell* 52:405-414 (1988); Roberts, A.B., *et al.*, *Proc. Natl. Acad. Sci. USA* 83:4167-4171 (1986); and, Ignotz, R.A., et al., *J. Biol., Chem.* 261:4337-4345 (1986), respectively.

The Office Action has also alleged that the claim language of claim 21 must be amended to reflect *in vitro* usage only because "Applicants have used the antibodies [to TGF-β] to cells grown in a petri dish and since such pathologies as glomerulonephritis, adult respiratory distress syndrome and cirrhosis of the liver are organismal ailments ..." the claims must be limited accordingly. Applicants respectfully traverse, maintaining that the disclosure enables use of the methods *in vivo*. Experiments disclosed in the Specification demonstrate that animals with induced kidney injury treated with anti-TGF-β antibody had less ECM than control-treated, injured animals.[24] Furthermore, levels of TGF-β RNA was examined in the kidneys of injured and control-treated rats. mRNA analysis revealed decreased levels of TGF-β mRNA in the nephritic (injured) rats, including the anti-TGF-β treated animals.[25] Furthermore, the Office Action acknowledges the *in vivo* experiments of the Specification, stating "[t]he specification further discloses a single treatment of rats with antibodies to TGF-beta followed by

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[24] Please see page 24, lines 3 to 16, and Figure 17, of the Specification. The "control-treated" animals were injected with normal rabbit serum (versus immune serum containing anti-TGF-β antibodies)

[25] Please see page 24, lines 18 to 29, of the Specification, and Van Obberghen-Schilling, et al., incorporated by reference.

examination of the removed glomeruli."[26] Accordingly, *in vivo* experiments sufficiently enable the claimed methods to satisfy the requirements of section 112, first paragraph, and the claims do not need to be limited to *in vitro* methods.

With respect to use of the claimed methods *in vivo*, Applicants maintain that the courts have held that art-recognized animal experimental models can show the usefulness of a method of treatment or a therapeutic composition to satisfy the requirements of section 112, first paragraph. For example, while the experiments in a specification may not satisfy the Food and Drug Administration's (FDA) criteria for commercial drug approval, the Federal Circuit has clearly stated that FDA approval is not a prerequisite for finding a composition useful within the meaning of the patent laws:[27]

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F.3d 1058, 1063, 32 USPQ2d (BNA) 1115, 1120.

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[26] Please see page 4, lines 15 to 16, of the June 2, 1994, Office Action.

[27] The court in *In re Brana*, evaluating "what must the applicant prove regarding the practical utility or usefulness of the invention" - a pharmaceutical composition, was citing *Scott*, 34 F.3d 1058, 1063, 32 USPQ2d (BNA) 1115, 1120, which evaluated the sufficiency of testing to show reduction to practice of a medical device. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436, 1439 (Fed. Cir. 1995).

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.[28]

Title 35 does not demand that such human testing occur within the confines of PTO proceedings.[29] Additionally, the Federal Circuit recently held that *in vivo* testing in rats was sufficient to constitute a reduction to practice of a method because the word "patient" was sufficiently broad to include the laboratory rats to whom the compounds were administered.[30]

The Office Action further alleges that "[t]here is no evidence presented in the Specification that the `pathology' *per se* has been treated since pathology is an on-going condition ... [t]here is no evidence that the single dose of antibody would cure the disease ... the Specification fails to disclose in

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[28] *In re Brana*, 34 USPQ2d at 1442.

[29] *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d (BNA) 1115, 1120 (Fed. Cir. 1994).

[30] *Fujikawa v. Wattanasin*, No. 95-1418, 95-1425, 1996 U.S. App. LEXIS 22414 at *9 (Fed. Cir. Aug. 28, 1996). The CAFC was analyzing the reduction to practice of a method count in an appealed interference proceeding; the interference pertained to a compound and a method for inhibiting cholesterol biosynthesis in humans and other animals.

detail the treatment regimen of the rats."[31] Applicants respectfully traverse. However, the instant claimed methods, as amended, claim do not claim to cure any pathology. The claims now read on a method of treating a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of an ECM component in a tissue; a method of decreasing the deleterious accumulation of a TGF-β-induced ECM component in a tissue; and, a method of decreasing the synthesis of a TGF-β by a cell in a tissue which produces the TGF-β. Because the claims now read on a method of decreasing or suppressing the deleterious accumulation of ECM, it is not necessary for the disclosure to enable a "treatment regimen"[32] or "evidence of long-term treatments and the effects of treatment with a foreign antibody"[33] to satisfy the requirements of section 112, first paragraph.

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[31] Please see pages 4 to 5, lines 13 to 30 and 1 to 8, respectively, of the June 2, 1994, Office Action.

[32] Please see page 4, lines 25 to 30, of the 6/2/94 Office Action.

[33] Please see page 5, lines 1 to 8, of the 6/2/94 Office Action.

Methods for Treating Pathologies Involving the Deleterious Accumulation of ECM other than Glomerulonephritis Have Utility and are Enabled

The Office Action further alleges that "the claims must be limited to glomerulonephritis, since Applicants have failed to show that the treatment using anti-TGF-β antibodies would be effective in the treatment of [cirrhosis of the liver and adult respiratory distress syndrome (RDS)]" because "[i]t is not apparent that cirrhosis of the liver and [RDS] would be amenable to treatment with antibodies to TGF-β since the etiology of many diseases is not known."[34] Applicants respectfully traverse, noting that the pathophysiology of RDS and cirrhosis are well known to the skilled artisan to include the deleterious accumulation of ECM.[35] The Patent Office has cited Gessner, A.M., *et al.*, *Eur. J. Clin. Chem. Clin. Biochem.* 29:293-311 (1991)[36] to rebut the presumptively correct assertions of utility in the disclosure with respect to the use of compositions which

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[34] Please see page 5, lines 9 to 18, of the 6/2/94 Office Action.

[35] To support this statement with scientific evidence, four papers were presented in an IDS submitted with Applicants response dated June 11, 1993, in the grandparent application no. 07/416,656; and discussed on pages 6 and 7 of that response. These publications clearly showed the relationship between accumulation of ECM and the pathophysiology of liver cirrhosis and RDS.

[36] Hereinafter "Gressner." Gressner entered into the record in the IDS submitted June 11, 1993.

decrease the activity of TGF-β to treat cirrhosis or RDS.[37] The Office Action cited Gessner for the proposition that in cirrhosis the pathobiology of the disease changes over time and therefore the use of anti-TGF-β agents to treat the disease is not established.[38] However, the methods of the invention do not claim to cure a disease or to treat all phases of a progressive, chronic disease, such as liver cirrhosis. Effective treatment can be in the form of decreasing the deleterious accumulation of ECM at any stage of the disease process, and this form of treatment is sufficiently disclosed in the Specification to satisfy the requirements of section 112, first paragraph.[39]

The Office Action has proffered no evidence that a skilled artisan could not practice the invention utilizing the disclosure and guidance from the state of the art by analogy or prior art teachings without undue experimentation, as it pertains

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[37] The Office Action has the initial burden of challenging a presumptively correct assertion of utility of the disclosure. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 439 F.2d 220, 223-224, 169 USPQ (BNA) 367, 369-70 (CCPA 1971). *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

[38] Please see page 3, lines 17 to 23, of the Office Action dated October 13, 1993, for application no. 07/416,656.

[39] Please see Applicants response on page 6, section B, dated February 11, 1994, in the parent application no. 08/196,892.

to a method of treating a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of an ECM in a tissue other than glomerulonephritis. No experimental data or scientific theories alleging that the invention is inherently unbelievable or involves implausible scientific principles has been presented. Accordingly, a *prima facie* case of nonenablement has not been established and the objection and rejection can properly be withdrawn.

It has also been alleged that because "Applicants have failed to demonstrate utility for the treatment of RDS and cirrhosis of the liver at any stage," methods for treating these pathologies are not enabled.[40] Applicants respectfully traverse. The Office Action has proffered no evidence that a skilled artisan could not practice the invention utilizing the disclosure and guidance from the state of the art by analogy or prior art teachings without undue experimentation, as it pertains to a method of treating RDS or cirrhosis of the liver. No experimental data or scientific theories alleging that the invention is inherently unbelievable or involves implausible scientific principles has been presented. Accordingly, a *prima facie* case of nonenablement has not been established and the objection and rejection can properly be withdrawn.

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[40] Please see page 5, lines 19 to 24, of the 6/2/94 Office Action.

However, assuming *arguendo* that the Patent Office may have met this initial burden, Applicants respectfully maintain that they are able to offer sufficient rebuttal evidence and argument to convince one of skill in the art that methods pertaining to the treatment of pathologies other than glomerulonephritis that the Specification satisfies section 112, first paragraph's requirements of operability and utility.

Applicants maintain that, based on the instant disclosure, one skilled in the art would reasonably expect that agents that can inhibit TGF-β activity would be efficacious in the treatment of any pathology which is characterized by the deleterious accumulation of ECM. Scientific evidence submitted and argued on the record clearly demonstrates that the deleterious accumulation of ECM contributes to tissue pathology associated with these diseases.[41] For example, Fausto states:

> TGF-β1 induces extracellular matrix formation and increases its stability by regulating the synthesis and degradation of matrix components ... During chronic liver disease it is likely that collagens are produce mainly by lipocytes .. TGF-β1 induces col I [procollagen type I] mRNA in cultured lipocytes ... Analysis of biopsies obtained

[41] Four papers were presented in an IDS submitted June 11, 1993, in application no. 07/416,656; and discussed on pages 6 and 7 of the response dated June 11, 1993.

> from 40 patients [with hepatic disease] and four control subjects demonstrated a significant correlation between steady-state levels of TGF-β1 and col I mRNAs in the liver."[42]

Furthermore, evidence presented in the instant Specification demonstrates that the ability to stimulate proteoglycan production is a relatively specific property of TGF-β and that tissues prone to pathological accumulation of ECM synthesize particular proteoglycans.[43] Thus, manipulating this specific effect of TGF-β has utility in controlling or treating the inappropriate and undesirable accumulation of ECM components in various pathologies.[44] The Specification teaches that the pathologies expressly noted are merely representative and a person skilled in the art would readily recognize the methods of the invention to be used in any pathology associated with accumulation of ECM.[45]

Accordingly, Applicants maintain that one skilled in the art would reasonably expect that administration of an agent

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[42] Please see page 172 of Fausto.

[43] For example, please see page 7, lines 26 to 24; and page 21, lines 9 to 22, of the Specification.

[44] Please see pages 7 and 8, lines 35 to 37 and 1 to 2, respectively, of the Specification.

[45] Please see page 9, lines 1 to 14, of the Specification.

which inhibits the activity of TGF-β would reduce the severity of a pathology characterized by the deleterious accumulation of ECM. One skilled in the art would accept the operability and utility of a method of treating a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of an extracellular matrix (ECM) component in a tissue; a method of decreasing the deleterious accumulation of a TGF-β-induced extracellular matrix component in a tissue; or, a method of decreasing the synthesis of a TGF-β by a cell in a tissue which produces the TGF-β, *in vivo*.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office Action has rejected claims 21 to 29 under 35 U.S.C. § 112, second paragraph, alleging that the disclosure fails to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.[46] Applicants respectfully traverse.

Specifically referring to claims 21 to 23 and 27 to 29, the Office Action alleges that the word "agent" is vague and

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[46] Please see page 2, lines 27 to 28, of the outstanding Office Action dated April 1, 1996, which maintained the rejection under section 112, second paragraph, set forth in the last Office Action dated June 2, 1994, for the parent, serial no. 08/196,892, on page 2, lines 22 to 26.

unclear since the nature of the agent is indeterminate. Applicants respectfully traverse.

The legal standard for definiteness under section 112, second paragraph, is whether a claim reasonably apprises those of skill in the art of its scope.[47] The law is clear that if the claims, read in light of the specification, reasonably apprises those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more.[48] The amount of detail required to be included in claims depends on the particular invention and the prior art, and is not to be viewed in the abstract but in conjunction with whether the specification is in compliance with the first paragraph of section 112.[49]

Applicants respectfully maintain that claims 21 to 23 and 27 to 29, read in light of the Specification, reasonably apprise those skilled in the art both of the utilization and

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[47] *In re Warmerdam*, 33 F.3d 1354,31 USPQ2d 1754, 1759 (*citing Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d at 1217, 18 USPQ2d at 1030).

[48] *North American Vaccine Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 28 USPQ 1333, 1339 (Fed. Cir. 1993) (*citing Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985), *cert. dismissed*, 474 U.S. 976 (1985).

[49] *Shatterproof Glass Corp.*, 225 USPQ at 641.

scope of the invention and thus particularly delineate the invention. Specifically, the term "agent" is described and defined in the Specification to delineate the full scope of the invention:

> Agents which inhibit TGF-β activity, such as antibodies reactive with TGF-β, have been found to block the stimulatory effect of TGF-β on proteoglycan production.[50] ... Moreover, agents which can block the effect of TGF-β, such as an antiserum, block the stimulatory effect of exogenous TGF-β. Such agents, including monoclonal and polyclonal antibodies, PDGF and Arg-Gly-Asp containing peptides, can be used to specifically control or treat deleterious matrix proteoglycan synthesis. Thus, such agents can be used to prevent any condition associated with extracellular matrix accumulation, for example scaring, or to treat pathologies characterized by an accumulation of extracellular matrix in a tissue by contacting the tissue with an agent which suppresses TGF-β activity.[51]

Accordingly, the claims incorporating the term "agent," when read in light of the Specification, reasonably apprise those

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[50] Please see page 7, lines 32 to 34, of the Specification.

[51] Please see pages 8 and 9, lines 31 to 37 and 1 to 6, respectively, of the Specification.

skilled in the art both of the utilization and scope of the invention and thus particularly delineate the invention.

Rejection of the Claims Under 35 U.S.C. § 102

Claim 27 stands rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Flanders, *et al.*, *Biochemistry* 27:739-746 (January, 1988).[52] Applicants respectfully traverse.

The Office Action alleges that Flanders discloses the use of the antibody to TGF-β to block TGF-β induced collagen production in normal rat kidney (NRK) cells; and, since the antibody to TGF-β decreases the amount of TGF-β, Flanders anticipates claim 27.[53] However, claims 27 claims a method of decreasing the deleterious accumulation of a TGF-β induced ECM component in a tissue, comprising contacting the tissue with an agent which decreases the activity of TGF-β; or contacting the tissue with an agent which inhibits the ECM component-inducing activity of TGF-β; whereby the decrease in the activity of the TGF-β decreases the deleterious accumulation of the ECM

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[52] Hereinafter "Flanders." Please see page 2, lines 29 to 30, of the outstanding Office Action dated April 1, 1996, which maintained the rejection under section 102(b), set forth in the last Office Action dated June 2, 1994, for the parent, serial no. 08/196,892, on page 7, lines 19 to 24.

[53] Please see page 2, lines 29 and 30, of the outstanding Office Action, dated April 1, 1996; and page 7, lines 19 to 24, of the June 2, 1994, Office Action.

component; and whereby the agent is not a general protein synthesis inhibitor.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.[54] Specifically, Flanders teaches:

> The abilities of antisera to block TGF-β biological activity were evaluated in an assay that measures the TGF-β-induced production of collagen by NRK [rat kidney fibroblast] cells [grown in 24-well cluster dishes]. Both the antiserum raised to the TGF-β dimer and that raised to P 78-109 at IgG concentrations of 80 and 500 ug/mL, respectively, blocked over 90% of the increase in collagen production induced by 50 pM TGF-β. Anti-P at an IgG concentration of 500 ug/mL inhibited the increase by 40%.[55]

Flanders does not teach or suggest using anti-TGF-β antibody *in vivo* or in a tissue. Flanders does not teach or suggest the inhibition of TGF-β activity for the purpose of

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[54] Additionally, the reference must be enabling and describe the applicant's claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention. *In re Paulson*, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994)(*citing In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990)).

[55] Please see page 741, first column, "Inhibition of TGF-β-induced Collagen Production in NRK Cells by Antisera;" and, page 743, second column, second full paragraph, of Flanders.

decreasing the deleterious accumulation of ECM or any of its components, including collagen. Because Flanders' teaching is limited to the inhibition of collagen production by a cultured cell line, it is not a single prior source which contains each and every limitation of claim 27. Accordingly, the section 102, specifically the section 102(a), rejection against claim 27 can be properly withdrawn.

Rejection of the Claims Under 35 U.S.C. § 103

Claims 21 and 24 stand rejected under 35 U.S.C. § 103, as allegedly obvious over Conner, *et al.*, *J. Clin. Invest.* 83:1661-1666 (1989).[56] Applicants respectfully traverse.

However, a Declaration under 37 C.F.R. § 1.131 is submitted herewith as Exhibit B by Drs. Wayne Border and Erkki Rouslahti, the named inventors for this application. As stated in the Declaration, Drs. Border and Rouslahti conceived of the invention prior to the April 14, 1989, mailing date of the MacKay publication, which is the earliest of the cited references, and was diligently pursued until the filing of the application on

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[56] Hereinafter "Conner." Please see page 3, lines 1 to 3, of the outstanding Office Action dated April 1, 1996, which maintained this rejection under section 103, set forth in the last Office Action dated June 2, 1994, for the parent, serial no. 08/196,892, on pages 7 to 9, lines 25 to 27, 1 to 30 and 1 to 30, respectively.

October 3, 1989.[57] Thus, the cited references MacKay and Conner were not published before the invention by the Applicant and, therefore, are not prior art under 35 U.S.C. § 102(a). Accordingly, Applicants respectfully request the Examiner remove the rejection of claims 21 and 24 under 35 U.S.C. § 102.

Applicants make it of record that the Declaration has been submitted merely to expedite examination of the claims under consideration. Submission of this Declaration under 37 C.F.R. §1.131, Exhibit B, is neither a concession nor admission that claims 21 and 24 under examination are obvious over Conner.

Claims 22, 23, 25 and 26 stand rejected under 35 U.S.C. § 103, as allegedly obvious over Conner as applied to claims 21 and 24, in further view of Mackay, *et al., J. Clin. Invest.* 83:1160-1167 (1989).[58] Applicants respectfully traverse. However, the cited references MacKay and Conner were not published before the invention by the Applicant and, therefore, are not prior art under 35 U.S.C. § 102 (a). Accordingly, Applicants respectfully request the Examiner remove the rejection of claims 22, 23, 25 and 26 under 35 U.S.C. § 103.

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[57] U.S. patent application no. 07/416,656.

[58] Hereinafter "Mackay." Please see page 3, lines 4 to 7, of the outstanding Office Action dated April 1, 1996, which maintained this rejection under section 103, set forth in the last Office Action dated June 2, 1994, for the parent, serial no. 08/196,892, on page 11, lines 3 to 21.

Applicants make it of record that the Declaration has been submitted merely to expedite examination of the claims under consideration. Submission of this Declaration under 37 C.F.R. §1.131, Exhibit B, is neither a concession nor admission that claims 22, 23, 25 and 26 under examination are obvious over Conner in further view of MacKay.

Claim 28 stands rejected under 35 U.S.C. § 103, as allegedly obvious over Flanders[59] as applied to claim 27 above and in further view of MacKay.[60] Applicants respectfully traverse. However, the cited reference MacKay was not published before the invention by the Applicant and, therefore, was not prior art under 35 U.S.C. § 102(a). Accordingly, Applicants respectfully request the Examiner remove the rejection of claim 28 under 35 U.S.C. § 103.

Applicants make it of record that the Declaration has been submitted merely to expedite examination of the claims under consideration. Submission of this Declaration under 37 C.F.R.

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[59] In fact, Flanders was cited in an anticipation, section 102(b), rejection, not a section 103 rejection.

[60] Please see page 3, lines 8 to 10, of the outstanding Office Action dated April 1, 1996, which maintained this rejection under section 103, set forth in the last Office Action dated June 2, 1994, for the parent, serial no. 08/196,892, on pages 7 to 9, lines 22 to 27, 1 to 30 and 1 to 30, respectively.

§1.131, Exhibit B, is neither a concession nor admission that claim 28 under examination is obvious over Flanders in further view of MacKay.

Claim 28 stands rejected under 35 U.S.C. § 103, as allegedly obvious over Flanders as applied to claim 27[61] above and in further view of Bassols, A., *et al., J. of Biol. Chem.* 263:3039-3045 (1988).[62] Applicants respectfully traverse.

Implicit in the section 103 rejection is that Flanders contains deficiencies that are cured by Bassols. Applicants will show that the deficiencies in Flanders are not cured by Bassols. Accordingly, a *prima facie* case of obviousness has not been established and the rejection should be properly withdrawn.

As noted above, Flanders is relied on for allegedly disclosing use of the antibody to TGF-β to block TGF-β-induced collagen production in NRK cells, collagen being another

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[61] Please note that claim 29 has been amended in the instant response to read on the method of claim 21 or 27 wherein the extracellular matrix component comprises proteoglycan. New claim 30 reads on the method of claim 29, wherein the proteoglycan is selected from the group consisting of biglycan and decorin.

[62] Hereinafter "Bassols." Please see page 3, lines 11 to 13, of the outstanding Office Action dated April 1, 1996, which maintained this rejection under section 103, set forth in the last Office Action dated June 2, 1994, for the parent, serial no. 08/196,892, on pages 12 to 13, lines 23 to 30 and 1 to 14, respectively.

proteoglycan.[63] While not expressing stating the deficiency in Flanders, the Office Action, using Bassols to cure the deficiency in Flanders, notes some of the deficiencies in Flanders by stating that Bassols discloses that NRK cells produce, in response to TGF-β, large amounts of the proteoglycans decorin and biglycan, and that it would have been obvious "in view of the teachings of Flanders that treatment of NRK cells with antibodies to TGF-β would likewise inhibit the production of biglycan and decorin as was seen with collagen."[64]

However, Applicants maintain that Flanders is also deficient in that it does not teach or suggest using anti-TGF-β antibody *in vivo* or in a tissue. Flanders does not teach or suggest the inhibition of TGF-β activity for the purpose of decreasing the deleterious accumulation of ECM or any of its components, including collagen. Flanders' teaching is limited to the inhibition of collagen production by a cultured cell line.

A *prima facie* case of obviousness is established only when the teaching from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary

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[63] However, while one skilled in the art would recognize that collagen is a component of the ECM, the artisan would not consider collagen to be a proteoglycan.

[64] Please see pages 12 to 13, lines 23 to 30 and 1 to 5, respectively, of the June 2, 1994, Office Action.

skill in the art. The art must suggest how to apply their teachings to the specifically claimed invention. Bassols makes not teach or suggest the use of any agent, including anti-TGF-β antibody, *in vivo* or in a tissue. Bassols does not teach or suggest the inhibition of TGF-β activity for the purpose of decreasing the deleterious accumulation of the ECM or any of its components, including collagen. Accordingly, Applicants respectfully assert that the combination of Flanders and Bassols do not teach or suggest how to invent a method for decreasing the deleterious accumulation of an ECM component in a tissue.

Accordingly, a case of *prima facie* obviousness has not been established. Applicants respectfully submit that in view of the above presented arguments, the rejection of the claims under 35 U.S.C. § 103 should be properly withdrawn.

CONCLUSION

In light of the foregoing remarks, it is believed that the Examiner may properly withdraw all objections to the Specification and rejections to the claims. It is further believed that the present application is now in condition for immediate allowance.

Applicants invite the Examiner to call the undersigned representative or Cathryn Campbell if there are any questions or if she believes an interview would be useful for any reason.

Respectfully submitted,

October 1, 1996
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